a gene according to claim 67 operably linked to the act I promoter of *S. coelicolor*, said host being a microorganism other than *S. coelicolor*; and

b. culturing said transformed host microorganism to effect synthesis of said polyketide.

Please add new claim 68, as follows:

68. (New) A hybrid PKS gene according to claim 67, wherein said at least one second nucleic acid portion endoces at least one extension module.

A marked-up copy of the present claim amendments is attached.

REMARKS

Prior to the issuance of a further Official Action in response to applicants' Request for Continued Examination (RCE) filed November 21, 2002 in the above-identified patent application, the Examiner is respectfully requested to take into account the Declaration of Professor Thomas James Simpson and the Declaration of Professor Jeremy Randall Knowles which are submitted herewith, as well as the present claim amendments.

Turning first to the present amendments, claim 26, 31, 35-37, 44, 47, 50, 51, 54-56 and 64 have been amended so as to

dependent from claim 67, which was presented with applicants' Second Supplemental Amendment and Request for Reconsideration filed April 24, 2003.

New claim 68 has been added, which is also dependent from claim 67 and which further characterizes the at least one second nucleic acid portion of the hybrid PKS gene of claim 67 as encoding at least one extension module. Support for new claim 67 is provided by original claim 2.

Claim 25 has been amended so as to be dependent from new claim 68.

Claims 33 and 34 have been amended so as to clarify that the promoter is the actI promoter.

The dependency of claim 39 has been amended to correct a transcription error made in a prior amendment. Claim 39 is once again dependent on claim 37.

Claims 25-27, 31-37, 39, 44 and 47-68 are believed to be in condition for allowance, as the various grounds of rejection set forth in the May 21, 2002 final rejection are inapplicable to these claims, as now amended.

Claim 67 calls for a hybrid PKS gene comprising a first nucleic acid portion encoding multiple domains of a first Type I PKS comprising at least a loading module lacking a ketosynthase (KS) activity and at least one second nucleic acid portion encoding at least one Type I PKS domain which is heterologous to said first Type I PKS. See page 6, line 15 through page 7, line 22 and Figure 2A of the present specification. The PKS gene of

claim 67 is neither taught nor suggested by the disclosure of Khosla '290, considered alone or in combination with Kao and/or Cox.

The Declaration of Professor Simpson and the Declaration of Professor Knowles submitted herewith clearly establish that the hybrid PKS gene of claim 67 is neither anticipated nor rendered obvious by the disclosure of Khosla '290. Both declarations set forth the state of the art pertaining to the generation and synthesis of Type I and Type II PKS molecules. Regarding the unique loading module called for in claim 67, the Declaration of Professor Simpson unequivocally states that the identification of the loading module as an autonomous module was not recognized or commented on in Khosla '290. The Declaration of Professor Knowles also speaks to the significance of the loading module of claim 67, stating that the prior art in general and Khosla '290 in particular does not describe or suggest a hybrid Type I PKS gene having a discrete loading module lacking KS activity. Selective use of the loading domains discovered by applicants enables the skilled person to selectively synthesize polyketides comprising altered starter units. See page 129, first full paragraph of the present specification.

In view of the Declaration of Professor Simpson and the Declaration of Professor Knowles, the reasons for rejecting claim 1-3, 25, 26, 31-37, 39, 44, 47-49 and 55-58 are clearly inapplicable to claim 67 and the claims dependent therefrom.

Regarding the obviousness rejection of claim 27 based on Khosla '290 and Kao and the obviousness rejection of claim 51 based on Khosla '290 and Cox, the citation of the Kao and Cox references fails to compensate for the above-noted fundamental deficiencies in the disclosure of Khosla '290, with respect to the failure to identically disclosure or describe applicants' hybrid PKS gene have the characteristics specified in claim 67, from which claims 27 and 51 now depend, either directly or indirectly. That being the case, the §103 rejections of claims 27 based on Khosla '290 and Kao and of claim 51, based on Khosla '290 and Cox, are untenable and should be withdrawn.

The rejections of claims 50 and 52-54 under §112, first paragraph based on alleged lack of written description, the rejection of claim 39 under §112, first paragraph based on alleged inadequate enablement and the rejection of claims 35 and 47 based on alleged double patenting are fully addressed in applicants' RCE. For the reasons stated therein, all of the last-mentioned three (3) grounds of rejection are untenable and should be withdrawn.

In view of the present amendments, the Declarations submitted herewith and the foregoing remarks, it is respectfully urged that the rejections set forth in the May 21, 2002 Official Action be withdrawn and that this application be passed to issue, and such action is earnestly solicited.

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Marked-Up Version of Amended Claims

25. (Amended) A hybrid PKS gene according to claim [2] 68 wherein said loading module is capable of loading a substrate to produce a starter unit different from a starter unit normally associated with said at least one extension module.

26. (Amended) A hybrid PKS gene according to claim [2] 67 wherein said loading module is capable of loading any of a multiplicity of different starter units.

31. (Twice Amended) A nucleic sequence encoding a gene according to claim [1] 67 operably linked to a PKS type II promoter.

33. (Twice Amended) A nucleic sequence according to claim 31, wherein the promoter is the act I promoter of S. coelicolor.

34. (Twice Amended) A nucleic sequence according to claim 32, wherein the promoter is the act I promoter of S. coelicolor.

35. (Amended) A hybrid polyketide synthase as encoded by a gene according to claim [1] 67.

36. (Amended) A vector including a gene according to claim [1] 67.

37. (Twice Amended) A transformed microorganism containing a gene according to claim [1] 67 and able to express a polyketide synthase encoded thereby.

39. (Thrice Amended) A method of making a polyketide by culturing the microorganism of claim [27] 37 wherein said microorganism is an actinomycete.

44. (Amended) A hybrid PKS gene according to claim [1] 67, wherein said first nucleic acid portion encodes at least a loading module which comprises an acyltransferase and an acyl carrier protein, and said second nucleic acid portion encodes at least one extension module.

47. (Amended) A plasmid comprising a gene according to claim [1] 67.

50. (Twice Amended) A plasmid comprising a gene according to claim [1] 67 which is adapted to integrate into a specific attachment site (att) of a host's chromosome.

51. (Amended) A method of producing a transformant microorganism comprising the steps of:

(a) producing a plasmid which comprises donor DNA which is a gene according to claim [1] 67, and

(b) transforming with said plasmid a microorganism having a chromosome including DNA which undergoes homologous recombination with said plasmid to integrate said gene into the chromosome.

54. (Twice Amended) A hybrid PKS gene according to claim [1] 67, wherein said first type I PKS naturally includes a thioesterase as a chain terminating enzyme, and wherein said hybrid gene includes a nucleic acid sequence encoding the enzyme from the rapamycin system which, in said rapamycin system, effects connection of the polyketide chain to an amino acid chain in place of said thioesterase.

55. (Amended) A transformed prokaryotic organism containing a gene according to claim [1] 67 and operable to express a polyketide synthase encoded thereby.

56. (Amended) A transformed microorganism which naturally expresses a polyketide synthase and which contains as a result of its transformation a gene according to claim [1] 67 and is operable to express a polyketide synthase encoded thereby.

64. (Amended) A method of making a polyketide comprising:

a. providing a transformed host microorganism containing a gene according to claim [1] 67 operably linked to the act I promoter of *S. coelicolor*, said host being a microorganism other than *S. coelicolor*; and

b. culturing said transformed host microorganism to effect synthesis of said polyketide.